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(54) **Controlled release formulation containing tramadol.**

(57) A controlled release preparation for oral administration contains tramadol, or a pharmaceutically acceptable salt thereof, as active ingredient.

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The present invention relates to a controlled release preparation for oral administration, to processes for its preparation and to its medical use. In particular, the invention relates to a controlled release preparation comprising tramadol or a pharmaceutically acceptable salt thereof.

Tramadol, which has the chemical name (±)-trans-2-[(dimethylamino)methyl]-1-(3-methoxyphenyl) cyclohexanol, is an orally active opioid analgesic. Conventional release preparations in the form of capsules, drops and suppositories containing tramadol, or more particularly its hydrochloride salt, have been commercially available for many years for use in the treatment of moderate to severe pain. Such preparations, however, do not provide a controlled release of the tramadol. Moreover, despite tramadol's long-standing use, controlled release preparations for oral administration containing tramadol as active ingredient have not even previously been described in the literature.

It is an object of the present invention to provide an oral controlled release tramadol preparation suitable for at least twelve-hourly (e.g. up to twenty-four hourly) administration for the treatment of pain.

The present invention therefore provides a controlled release preparation comprising tramadol or a pharmaceutically acceptable salt thereof for oral administration.

Suitable pharmaceutically acceptable salts of tramadol for use according to the present invention are those conventionally known in the art such as pharmaceutically acceptable acid addition salts. The hydrochloride salt is particularly preferred.

A controlled release preparation according to the present invention is one that achieves slow release of a drug over an extended period of time, thereby extending the duration of drug action over that achieved by conventional delivery. Preferably such a preparation maintains a drug concentration in the blood within the therapeutic range for 12 hours or more.

The present inventors have found that in order to allow for controlled release tramadol over at least a twelve hour period following oral administration, the in vitro release rate preferably corresponds to the following % rate of tramadol released:

TABLE 1

TIME (H)	% RELEASED
1	0-50
2	0-75
4	3-95
8	10-100
12	20-100
16	30-100
24	50-100
36	>80

Another preferred preparation especially suited for twice-a-day dosing has an in vitro release rate corresponding to the following % rate of tramadol released:

TABLE 2

TIME (H)	% RELEASED
1	20-50
2	40-75
4	60-95
8	80-100
12	90-100

Yet another preferred preparation particularly suited for once-a-day dosing has an in-vitro release rate corresponding to the following % rate of tramadol released:

TABLE 3

TIME (H)	% RELEASED
1	0-50
2	0-75
4	10-95
8	35-100
12	55-100
16	70-100
24	>90

A still further preferred preparation in accordance with the invention also particularly suited for once-a-day dosing has an in vitro release rate corresponding to the following % rate of tramadol released.

TABLE 4

TIME (H)	% RELEASED
1	0-30
2	0-40
4	3-55
8	10-65
12	20-75
16	30-88
24	50-100
36	>80

More preferably a preparation for once-a-day dosing has an in vitro release rate substantially as follows:

TABLE 5

TIME (H)	% TRAMADOL RELEASED
1	10-30
2	17-37
4	27-47
8	40-60
12	49-69
16	57-77

Another preferred dissolution rate in vitro upon release of the controlled release preparation for administration twice daily according to the invention, is between 5 and 50% (by weight) tramadol released after 1 hour, between 10 and 75% (by weight) tramadol released after 2 hours, between 20 and 95% (by weight) tramadol

released after 4 hours, between 40 and 100% (by weight) tramadol released after 8 hours, more than 50% (by weight) tramadol released after 12 hours, more than 70% (by weight) released after 16 hours and more than 80% (by weight) tramadol released after 24 hours.

Furthermore, it is preferred in the case of a controlled release preparation for administration twice daily that after 8 hours following oral administration between 70 and 95% (by weight) tramadol is absorbed in vivo, between 77 and 97% (by weight) tramadol is absorbed after 10 hours and between 80 and 100% (by weight) tramadol is absorbed after 12 hours.

A formulation in accordance with the invention suitable for twice-a-day dosing may have a tmax of 1.5 to 8 hours, preferably 2 to 7 hours, and a W_{50} value in the range 7 to 16 hours.

A formulation in accordance with the invention suitable for once-a-day dosing may have a tmax in the range of 3 to 6 hours, preferably 4 to 5 hours and a W_{50} value in the range of 10 to 33 hours.

The W_{50} parameter defines the width of the plasma profile at 50% Cmax, i.e. the duration over which the plasma concentrations are equal to or greater than 50% of the peak concentration. The parameter is determined by linear interpolation of the observed data and represents the difference in time between the first (or only) upslope crossing and the last (or only) downslope crossing in the plasma profile.

The in vitro release rates mentioned herein are, except where otherwise specified, those obtained by measurement using the Ph. Eur. Paddle Method at 100rpm in 900ml 0.1 N hydrochloric acid at 37°C and using UV detection at 270nm.

The controlled release preparation according to the invention preferably contains an analgesically effective amount of tramadol or a pharmaceutically acceptable salt thereof, conveniently in the range of from 50 to 800 mg, especially 100, 200, 300, 400 to 600 mg (calculated as tramadol hydrochloride) per dosage unit.

The controlled release preparation according to the invention may be presented, for example, as granules, spheroids, pellets, multiparticulates, capsules, tablets, sachets, controlled release suspensions, or in any other suitable dosage form incorporating such granules, spheroids, pellets or multiparticulates.

The active ingredient in the preparation according to the invention may suitably be incorporated in a matrix. This may be any matrix that affords controlled release tramadol over at least a twelve hour period and preferably that affords in-vitro dissolution rates and in vivo absorption rates of tramadol within the ranges specified above. Preferably the matrix is a controlled release matrix. Alternatively, normal release matrices having a coating which provides for controlled release of the active ingredient may be used.

Suitable materials for inclusion in a controlled release matrix include

(a) Hydrophilic or hydrophobic polymers, such as gums, cellulose ethers, acrylic resins and protein derived materials. Of these polymers, the cellulose ethers, especially alkylcelluloses are preferred. The preparation may conveniently contain between 1% and 80% (by weight) of one or more hydrophillic or hydrophobic polymers.

(b) Digestible, long chain (C_8-C_{50}, especially C_{12}-C_{40}), substituted or unsubstituted hydrocarbons, such as fatty acids, fatty alcohols, glyceryl esters of fatty acids, mineral and vegetable oils and waxes. Hydrocarbons having a melting point of between 25 and 90°C are preferred. Of these long chain hydrocarbon materials, fatty (aliphatic) alcohols are preferred. The preparation may conveniently contain up to 60% (by weight) of at least one digestible, long chain hydrocarbon.

(c) Polyalkylene glycols. The preparation may suitably contain up to 60% (by weight) of one or more polyalkylene glycols.

One particularly suitable controlled release matrix comprises one or more alkylceluloses and one or more C_{12}-C_{36} aliphatic alcohols. The alkylcellulose is preferably C_1-C_6 alkyl cellulose, especially ethyl cellulose. The controlled release preparation according to the invention preferably contains from 1 to 20% (by weight), especially from 2 to 15% (by weight) of one or more alkylcelluloses.

The aliphatic alcohol may conveniently be lauryl alcohol, myristyl alcohol or stearyl alcohol but is preferably cetyl alcohol or more preferably cetostearyl alcohol. The controlled release preparation suitably contains from 5 to 30% (by weight) of aliphatic alcohol, especially from 10 to 25% (by weight) of aliphatic alcohol.

Optionally the controlled release matrix may also contain other pharmaceutically acceptable ingredients which are conventional in the pharmaceutical art such as diluents, lubricants, binders, granulating aids, colourants, flavourants, surfactants, pH adjusters, anti-adherents and glidants, e.g. dibutyl sebacate, ammonium hydroxide, oleic acid and colloidal silica.

The controlled release preparation according to the invention may conveniently be film coated using any film coating material conventional in the pharmaceutical art. Preferably an aqueous film coating is used.

Alternatively, the controlled release preparation according to this invention may comprise a normal release matrix having a controlled release coating. Preferably the preparation comprises film coated spheroids containing the active ingredient and a spheronising agent.

The spheronising agent may be any suitable pharmaceutically acceptable material which may be spher-

onised together with the active ingredient to form spheroids. A preferred spheronising agent is microcrystalline cellulose. The microcrystalline cellulose used may suitably be, for example, Avicel PH 101 or Avicel PH 102 (Trade Marks, FMC Corporation).

Optionally the spheroids may contain other pharmaceutically acceptable ingredients conventional in the pharmaceutical art such as binders, bulking agents and colourants. Suitable binders include water soluble polymers, water soluble hydroxyalkyl celluloses such as hydroxypropylcellulose or water insoluble polymers (which may also contribute controlled release properties) such as acrylic polymers or copolymers for example ethylcellulose. Suitable bulking agents include lactose.

The spheroids are coated with a material which permits release of the active ingredient at a controlled rate in an aqueous medium. Suitable controlled release coating materials include water insoluble waxes and polymers such as polymethacrylates (for example Eudragit polymers, Trade Mark) or water insoluble celluloses, particularly ethylcellulose. Optionally, water soluble polymers such as polyvinylpyrrolidone or water soluble celluloses such as hydroxypropylmethylcellulose or hydroxypropylcellulose may be included. Optionally other water soluble agents such as polysorbate 80 may be added.

Alternatively the drug may be coated onto inert non-pareil beads and the drug loaded beads coated with a material which permits control of the release of the active ingredient into the aqueous medium.

In a further aspect the present invention provides a process for preparing a controlled release preparation according to the present invention comprising incorporating tramadol or a pharmaceutically acceptable salt thereof in a controlled release matrix, for example by

(a) granulating a mixture comprising tramadol or a pharmaceutically acceptable salt thereof and one or more alkylcelluloses,

(b) mixing the alkylcellulose containing granules with one or more C_{12-36} aliphatic alcohols; and optionally

(c) shaping and compressing the granules, and film coating, if desired; or

(d) granulating a mixture comprising tramadol or a pharmaceutically acceptable salt thereof, lactose and one or more alkylcelluloses with one or more C_{12-36} aliphatic alcohol; and, optionally,

(e) shaping and compressing the granules, and film coating, if desired.

The controlled release preparation according to the invention may also be prepared in the form of film coated spheroids by

(a) granulating the mixture comprising tramadol or a pharmaceutically acceptable salt thereof and a spheronising agent;

(b) extruding the granulated mixture to give an extrudate;

(c) spheronising the extrudate until spheroids are formed, and

(d) coating the spheroids with a film coat.

One preferred form of unit dose form in accordance with the invention comprises a capsule filled with controlled release particles essentially comprising the active ingredient, a hydrophobic fusible carrier or diluent and optionally a hydrophillic release modifier. In particular, the controlled release particles are preferably prepared by a process which comprises forming a mixture of dry active ingredient and fusible release control materials followed by mechanically working the mixture in a high speed mixer with an energy input sufficient to melt or soften the fusible material whereby it forms particles with the active ingredient. The resultant particles, after cooling, are suitably sieved to give particles having a size range from 0.1 to 3.0mm, preferably 0.25 to 2.0mm. An example according to the invention is described below which is suitable for the commercial production of dosage units.

When using such a processing technique it has been found that, in order most readily to achieve the desired release characteristics (both in vivo and in vitro as discussed above) the composition to be processed should comprises two essential ingredients namely:

(a) tramadol or salt thereof; and

(b) hydrophobic fusible carrier or diluent; optionally together with

(c) a release control component comprising a water-soluble fusible material or a particulate soluble or insoluble organic or inorganic material.

We have found that the total amount of tramadol or pharmaceutically acceptable salt thereof in the composition may vary within wide limits, for example from 10 to 90% by weight thereof.

The hydrophobic fusible component (b) should be a hydrophobic material such as a natural or synthetic wax or oil, for example hydrogenated vegetable oil, hydrogenated castor oil, microcrystalline wax, Beeswax, Carnaubs wax or glyceryl monostearate, and suitably has a melting point of from 35 to 140°C, preferably 45 to 110°C.

The release modifying component (c), when a water soluble fusible material, is conveniently a polyethylene glycol and, when a particulate material, is conveniently a pharmaceutically acceptable material such as

dicalcium phosphate or lactose.

Another preferred process for the manufacture of a formulation in accordance with the invention comprises (a) mechanically working in a high-speed mixer, a mixture of tramadol or a pharmaceutically acceptable salt in particulate form and a particulate, hydrophobic fusible carrier or diluent having a melting point from 35 to 140°C and optionally a release control component comprising a water soluble fusible material, or a particulate soluble or insoluble organic or inorganic material at a speed and energy input which allows the carrier or diluent to melt or soften, whereby it forms agglomerates,

(b) breaking down the larger agglomerates to give controlled release seads; and

(c) continuing mechanically working with optionally a further addition of low percentage of the carrier or diluent.

(d) optionally repeating steps (c) and possibly (b) one or more times.

This process is capable of giving a high yield (over 80%) of particles in a desired size range, with a desired uniformity of release rate of tramadol or salt thereof.

The resulting particles may be sieved to eliminate any over-or undersized material then formed into the desired dosage units by for example, encapsulation into hard gelatin capsules containing the required dose of the active substance or by compression into tablets.

In this method in accordance with the invention preferably all the tramadol or salt thereof is added in step (a) together with a major portion of the hydrophobic fusible release control material used. Preferably the amount of fusible release control material added in step (a) is between 10% and 90% w/w of the total amount of ingredients added in the entire manufacturing operation, more preferably between 20% and 70% w/w.

Stage (a) of the process may be carried out in conventional high speed mixers with a standard stainless steel interior, e.g. a Collette Vactron 75 or equivalent mixer. The mixture is processed until a bed temperature about 40°C or above is achieved and the resulting mixture acquires a cohesive granular texture, with particle sizes ranging from about 1-3mm to fine powder in the case of non-aggregated original material. Such material, in the case of the embodiments described below, has the appearance of agglomerates which upon cooling below 40°C have structural integrity and resistance to crushing between the fingers. At this stage the agglomerates are of an irregular size, shape and appearance.

The agglomerates are preferably allowed to cool. The temperature to which it cools is not critical and a temperature in the range room temperature to 37°C may be conveniently used.

The agglomerates are broken down by any suitable means, which will comminute oversize agglomerates and produce a mixture of powder and small particles preferably with a diameter under 2mm. It is currently preferred to carry out the classification using a Jackson Crockatt granulator using a suitable sized mesh, or a Comil with an appropriate sized screen. We have found that if too small a mesh size is used in the aforementioned apparatus the agglomerates melting under the action of the beater or impeller will clog the mesh and prevent further throughput of mixture, thus reducing yield. A mesh size of 12 has been found adequate.

The classified material is returned to the high speed mixer and processing continued.

It is believed that this leads to cementation of the finer particles into particles of uniform size range.

In one preferred form of the method of the invention processing of the classified materials is continued, until the hydrophobic fusible materials used begin to soften/melt and optionally additional hydrophobic fusible material is then added. Mixing is continued until the mixture has been transformed into particles of the desired predetermined size range.

In order to ensure uniform energy input into the ingredients in the high speed mixer it is preferred to supply at least part of the energy by means of microwave energy.

Energy may also be delivered through other means such as by a heating jacket or via the mixer impeller and chopper blades.

After the particles have been formed they are cooled or allowed to cool, and may then be sieved to remove any over or undersized material.

The resulting particles may be used to prepare dosage units in accordance with the invention in the form of e.g. tablets or capsules in manners known per se.

We have also found that particles containing tramadol or a salt thereof produced by a melt processing as described in application PCT/SE93/00225 and the process described and claimed in our prior unpublished UK application No. 9324045.5 filed on 23 November 1993 as well as the process described herein are particularly useful for processing into the form of tablets.

We have found that by suitable selection of the materials used in forming the particles and in the tabletting and the proportions in which they are used, enables a significant degree of control in the ultimate dissolution and release rates of the tramadol or salt thereof from the compressed tablets.

Usually, to form a tablet in accordance with the invention, particles prepared as described above will be admixed with tabletting excipients e.g. one or more of the standard excipients such as diluents, lubricants,

binding agents, flow aids, disintegrating agents, surface active agents or water soluble polymeric materials.

Suitable diluents are e.g. microcrystalline cellulose, lactose and dicalcium phosphate. Suitable lubricants are e.g. magnesium stearate and sodium stearyl fumarate.

Suitable binding agents are e.g. hydroxypropyl methyl cellulose, polyvidone and methyl cellulose.

Suitable disintegrating agents are starch, sodium starch glycolate, crospovidone and croscarmalose sodium.

Suitable surface active are Poloxamer 188®, polysorbate 80 and sodium lauryl sulfate.

Suitable flow aids are talc colloidal anhydrous silica.

Suitable water soluble polymers are PEG with molecular weights in the range 1000 to 6000.

To produce tablets in accordance with the invention, particles produced in accordance with the invention may be mixed or blended with the desired excipient(s), if any, using conventional procedures, e.g. using a V-Cone or bin-blender and the resulting mixture compressed according to conventional tabletting procedure using a suitable size tabletting mould. Tablets can be produced using conventional tabletting machines, and in the embodiments described below were produced on standard single punch F3 Manesty machine or Killian RLE15 rotary tablet machine.

Generally speaking we find that even with such a highly water soluble active agent as tramadol or salt thereof tablets formed by compression according to standard methods give very low release rates of the active ingredient e.g. corresponding to release over a period of greater than 24 hours, say more than 36. We have found that the release profile can be adjusted in a number of ways. For instance a higher loading of the drug will be associated with increased release rates; the use of larger proportions of the water soluble fusible material in the particles or surface active agent in the tabletting formulation will also be associated with a higher release rate of the active ingredient. By controlling the relative amounts of these ingredients it is possible to adjust the release profile of the tramadol or salt thereof.

In order that the invention may be well understood the following examples are given by way of illustration only.

Example 1

Tablets having the following formulation were prepared:

	mg/tablet
Tramadol Hydrochloride	100
Lactose Ph. Eur.	68.0
Ethylcellulose (Surelease® 25% solids)	15
Purified Water Ph. Eur.	13.3*
Cetostearyl Alcohol Ph. Eur. (Dehydag wax 0)	42.00
Magnesium Stearate Ph. Eur.	2.00
Purified Talc Ph. Eur.	3.00
	230.00

* Removed during processing.

Tramadol hydrochloride (100mg) and lactose (68mg) were granulated, transferred to a fluid bed granulator and sprayed with ethylcellulose (15mg) and water. The granules were then dried at 60°C and passed through a 1mm screen.

To the warmed tramadol containing granules was added molten cetostearyl alcohol (42mg) and the whole was mixed thoroughly. The granules were allowed to cool and sieved through a 1.6mm screen. Purified talc and magnesium stearate were added and mixed with the granules. The granules were then compressed into tablets.

The tablets were coated with a film coat having the formulation given below.

	mg/tablet
Hydropropylmethylcellulose Ph. Eur. 15 cps (Methocel E15)	0.770
Hydroxypropylmethylcellulose (Ph. Eur. 5 cps (Methocel E5)	3.87
Opaspray M-1-7111B (33% solids)	2.57
Polyethylene glycol 400 USNF	0.520
Purified Talc Ph. Eur.	0.270
Purified Water Ph. Eur.	55.52*

* Remove during processing.

Example 2

Tablets having the following formulation were prepared:

	mg/tablet
Tramadol hydrochloride	100.0
Lactose Ph. Eur.	58.0
Ethylcellulose USNF (Ethocel 45 CP)	15.0
Cetostearyl alcohol Ph. Eur. (Dehydag wax O)	52.0
Magnesium stearate Ph. Eur.	2.00
Purified talc Ph. Eur.	3.00

A mixture of tramadol hydrochloride (100mg), lactose (58mg) and ethylcellulose (15mg) was granulated whilst adding molten cetostearyl alcohol (52mg) and the whole was mixed thoroughly. The granules were allowed to cool and sieved through a 1.6mm screen. Purified talc and magnesium stearate were added and mixed with the granules. The granules were then compressed into tablets which were coated with a film coat having the formulation given in Example 1.

Example 3

Film coated tablets were produced following the procedure described in Example 2 and having the following formulation:

	mg/tablet
Tramadol hydrochloride	100.00
Lactose Ph. Eur.	70.50
Hydroxyethylcellulose Ph. Eur.	12.50
Cetostearyl alcohol Ph. Eur.	42.00
Magnesium stearate Ph. Eur.	2.00
Purified talc Ph. Eur.	3.00

In vitro dissolution studies

In vitro dissolution studies were conducted on tablets prepared as described above. Results are given in Table 1.

TABLE 1

WT % TRAMADOL RELEASED

Time (h)	Example 1	Example 2*	Example 3
1	39	35	43
2	52	47	60
4	67	62	84
8	82	78	97
12	90	86	-

* Measured on tablet core

In a trial involving 12 healthy volunteers the serum levels of tramadol following administration of one tablet according to Example 2 was found to be as illustrated in Figure 1.

Example 4 and 5

Particles having the formulations given in Table II below , were prepared by the steps of:

i. Placing the ingredients (a) and (c) (total batch weight 0.7kg) in the bowl of a 10 litre capacity Collette Gral Mixer (or equivalent) equipped with variable speed mixing and granulating blades;

ii. Mixing the ingredients at about 150-1000rpm whilst applying heat until the contents of the bowl are agglomerated.

iii. Classifying the agglomerated material by passage through a Comil and/or Jackson Crockatt to obtain controlled release seeds.

iv. Warming and mixing the classified material in the bowl of a 10 litre Collette Gral, until uniform multiparticulates of the desired pre-determined size range are formed in yield of greater than 80%. This takes approximately 5 minutes.

v. Discharging the multiparticulates from the mixer and sieving them to separate out the multiparticulates collected between 0.5 and 2mm aperture sieves.

TABLE II		
Example	4	5
(a) Tramadol HCl (Wt%)	50	75
(b) Hydrogenated Vegetable Oil (Wt%)	50	25

Example 6

Samples of the particles from Example 4 were blended with magnesium stearate and purified talc using a Y-Cone or bin-blender. The blended mixture was then compressed using either (1) 14 x 6mm, (2) 16 x 7mm or (3) 18.6 x 7.5mm capsule shaped tooling on a single punch F3 Manesty tabletting machine to give tablets giving 200, 300 and 400mg of tramadol HCl. The ingredients per dosage unit amounted to the following:

TABLE III			
TABLET INGREDIENT	MG/TABLET		
	1	2	3
Tramadol Hcl	200	300	400
Hydrogenated Vegetable Oil	200	300	400
Sub Total	400	600	800
Purified Talc	12.63	18.95	25.26
Magnesium Stearate	8.42	12.63	16.84

The tablets were assessed by the dissolution using Ph. Eur. Paddle Method 100 rpm, 0.1 N HCl.
To assess the non-compressed particles the Ph Eur. Paddle was replaced by a modified Ph Eur. Basket.
The results are shown in Table IV below:

TABLE IV

HOURS AFTER START OF TEST	Particles	Tablet 1	Tablet 2	Tablet 3
	% TRAMADOL HCl RELEASED			
1	64	16	15	15
2	68	23	20	21
3	76	28	25	25
4	82	32	28	28
6	89	40	35	35
8	93	46	41	40
10	96	50	45	45
12	98	55	49	49
16	100	63	57	56
20	NR	70	63	NR

These results confirm the effectiveness of the tabletting in reducing the release rate.

Example 7

Samples of the particles from Example 5 were then tabletted using a procedure similar to Example 3 and the ingredients per unit dosage amounted to:

TABLE V

TABLET INGREDIENT	MG/TABLET		
	4	5	6
Tramadol Hcl	200	300	400
Hydrogenated Vegetable Oil	66.7	100	133
Sub Total	266.7	400	533
Purified Talc	7.63	11.44	15.25
Magnesium Stearate	5.16	7.63	10.17

The tablets and samples of non-compressed multiparticulates (each sample containing 400mg of tramadol hydrochloride) were assessed by the dissolution method also described above. The results are shown in Table VI below:

TABLE VI

HOURS AFTER START OF TEST	Particles	Tablet 4	Tablet 5	Tablet 6
	% TRAMADOL HCl RELEASED			
1	77	43	49	42
2	92	64	55	56
3	98	75	65	66
4	100	83	72	73
6	102	94	83	84
8	102	100	91	91
10	102	NR	96	97

These results show that by increasing the loading of the highly water soluble tramadol hydrochloride (75% w/w in this example compared with 50% w/w in Example 6) a significantly faster release rate of the active ingredient can be achieved.

Example 8

Example 4 was repeated but with the following formulation:

Tramadol HCl	200 mg/tablet
Hydrogenated Vegetable Oil	163.0 mg/tablet

The resulting multiparticulates were blended as described in Example 6 with the following:

Purified Talc	11.5 mg/tablet
Magnesium Stearate	7.66 mg/tablet

The blend was then compressed as described in Example 6 but using 15mm x 6.5mm normal concave capsule shaped plain/plain punches.

The resulting tablets were then assessed by the dissolution method described above. The results are shown in Table V.

HOURS AFTER START OF TEST	% TRAMADOL HCl RELEASED
1	20
2	27
3	32
4	37
6	44
8	50
10	55
12	60
16	67
20	73
24	77

In a trial involving five healthy male volunteers the plasma profile resulting from single dose administrations of the above tablet are shown in Figure 2 in comparison to the administration of a commercial preparation of Tramadol drops 100mg.

Claims

1. A controlled release preparation comprising tramadol or a pharmaceutically acceptable salt thereof for oral administration.

2. A controlled release preparation as claimed in Claim 1 containing from 50 to 800mg of tramadol (calculated as tramadol hydrochloride).

3. A controlled release preparation as claimed in Claim 1 or 2, having an in vitro dissolution rate (measured as herein defined) as set forth below:

TIME (H)	% RELEASED
1	0-50
2	0-75
4	3-95
8	10-100
12	20-100
16	30-100
24	50-100
36	>80

4. A controlled release preparation as claimed in Claim 1 or 2, having and in-vitro dissolution rate (measured as hereintdefined) as set forth below:

TIME (H)	% RELEASED
1	20-50
2	40-75
4	60-95
8	80-100
12	90-100

5. A controlled release preparation as claimed in Claim 1 or 2, having an in vitro dissolution rate (measured as hereinbefore defined) as set forth below:

TIME (H)	% RELEASED
1	0-50
2	0-75
4	10-95
8	35-100
12	55-100
16	70-100
24	>90

6. A controlled release preparation as claimed in Claim 1 or 2, having an in-vitro dissolution rate (measured as herein defined) as set forth below:

TIME (H)	% RELEASED
1	0-30
2	0-40
4	3-55
8	10-65
12	20-75
16	30-88
24	50-100
36	>80

7. A solid, controlled release oral dosage form according to any one of Claims 1 to 6 comprising a therapeutically effective amount of tramadol or a salt thereof in a matrix adapted to provide a controlled release of the tramadol or salt thereof upon oral administration.

8. A dosage form according to any one of Claim 7 characterised in that the matrix comprises a controlled release matrix comprising at least one alkyl, preferably C_1 to C_8 alkyl, cellulose, at least one C_{12} to C_{36}, preferably C_{14} to C_{22}, aliphatic alcohol and, optionally at least one polyalkylglycol, preferably polyethylene glycol.

9. A dosage form according to Claim 8, characterised in that the at least one alkylcellulose is ethylcellulose.

10. A dosage form according to Claim 8 or 9, characterised in that the dosage form contains from 1 to 20% w/w, preferably 2 to 15% w/w of one or more alkylcelluloses.

11. A dosage form according to any one of Claims 8 to 10, characterised in that the aliphatic alcohol comprises lauryl alcohol, myristyl alcohol, stearylalcohol, or preferably cetyl alcohol or cetostearyl alcohol.

12. A process according to any one of Claims 8 to 11, characterised in that the dosage form contains from 5 to 50% w/w of aliphatic alcohol, preferably from 10 to 25% w/w of aliphatic alcohol.

13. A dosage form according to any one of Claims 1 to 6, in the form of film coated spheroids, characterised in that the spheroid matrix comprises a spheronising agent, preferably microcrystalline cellulose.

14. A dosage form according to any one of Claim 1 to 6, in the form of multiparticulates wherein the matrix comprises a hydrophobic fusible carrier or diluent having a melting point from 35 to 140°C and optionally a release control component comprising a water soluble fusible material, or a particulate soluble or insoluble organic or inorganic material.

15. A dosage form according to any one of Claims 1 to 6, which comprises a tablet formed by compressing a multiparticulate according to Claim 14.

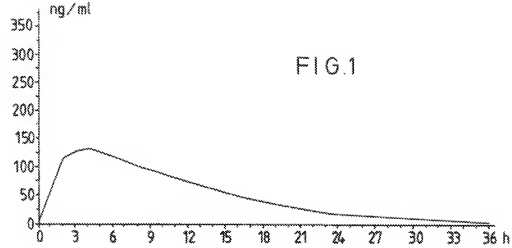
ng/ml
350
300
250
200
150
100
50
0
0
3
6
9
12
15
18
21
24
27
30
33
36 h

FIG.1

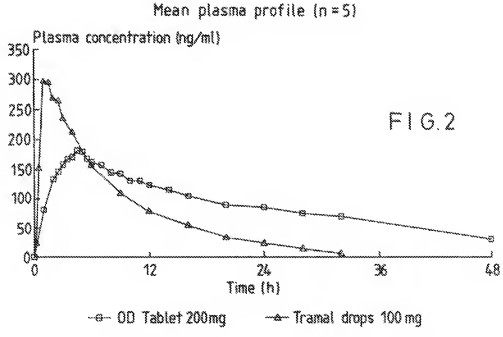
Mean plasma profile (n=5)
Plasma concentration (ng/ml)
350
300
250
200
150
100
50
0
0
12
24
36
48
Time (h)
OD Tablet 200mg
Tramal drops 100 mg

FIG.2

European Patent Office

EUROPEAN SEARCH REPORT

Application Number
EP 94 30 3128

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int.Cl.5)
X	EP-A-0 147 780 (MERCK & CO. INC.) * claims 1,2,8 * * page 2, line 31 - line 33 * * page 4, line 1 - line 6 * * page 10, line 8 - line 9 *	1,2	A61K31/135 A61K9/16 A61K9/20
A	CHEMICAL ABSTRACTS, vol. 112, no. 10, 5 March 1990, Columbus, Ohio, US; abstract no. 84206, * abstract * & JP-A-01 149 717 (SHOWA DENKO K.K.) 12 June 1989	1-6	
			TECHNICAL FIELDS SEARCHED (Int.Cl.5) A61K

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
THE HAGUE	19 August 1994	Scarponi, U

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
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